AMENDMENTS TO THE SPECIFICATION

Please amend the specification as shown.

Please delete paragraph [0010] and replace it with the following paragraph:

[0010] The invention also provides for isolated and/or purified antibodies (including both exogenous and endogenous) which specifically recognize the amino acid sequences comprising RSATEEEPPNDD **(SEQ ID NO: 1)** and/or DVEDSYGQQWTYEQR **(SEQ ID NO: 2)** of the α-subunit of $(Na^+ + K^+)$-ATPase enzyme. The binding of the antibodies to these amino acid sequences of the α-subunit of $(Na^+ + K^+)$-ATPase increase cardiac contraction and myocyte intracellular diastolic and systolic calcium.

Please delete paragraph [0013] and replace it with the following paragraph:

[0013] The invention also provides for isolated and/or purified peptides comprising the amino acid sequence RSATEEEPPNDD **(SEQ ID NO: 1)** and DVEDSYGQQWTYEQR **(SEQ ID NO: 2)** or derivatives thereof (including isoforms), which are used to generate inotropic antibodies when administered in vivo to a patient suffering from or susceptible to heart disease and/or myocyte contractile disorders. These peptides can be administered individually or in combination in a pharmaceutically acceptable carrier to a patient. Preferred isoforms of such peptides (i.e. comprising the sequence RSATEEEPPNDD **(SEQ ID NO: 1)** or DVEDSYGQQWTYEQR **(SEQ ID NO: 2)**) will also will generate such antibodies and preferably will comprise an amino acid sequence that has only 1, 2, 3, 4, 5, 6, 7 or 8 total amino acid differences from the sequence of RSATEEEPPNDD **(SEQ ID NO: 1)** or DVEDSYGQQWTYEQR **(SEQ ID NO: 2)**, more preferably will comprise an amino acid sequence that has only 1, 2, 3, or 4 total amino acid differences from the sequence of RSATEEEPPNDD **(SEQ ID NO: 1)** or DVEDSYGQQWTYEQR **(SEQ ID NO: 2)**.

Please delete paragraph [0016] and replace it with the following paragraph:

[0016] In another preferred embodiment, the invention provides for vectors which encode the amino acid sequences RSATEEEPPNDD **(SEQ ID NO: 1)**, DVEDSYGQQWTYEQR **(SEQ ID NO: 2)** or isoforms (derivatives) thereof, are used to generate inotropic antibodies when administered in vivo to a patient suffering from or susceptible to heart disease and/or myocyte contractile disorders. Preferably these vectors are under the control of tissue specific promoters, in particular, cardiac tissue specific. These peptides are administered as a vaccine to a patient in need of such therapy, in order to generate endogenous inotropic antibodies.

Please delete paragraph [0031] and replace it with the following paragraph:

[0031] The invention also provides for identifying molecules which target and block the RSATEEEPPNDD **(SEQ ID NO: 1)** and/or DVEDSYGQQWTYEQR **(SEQ ID NO: 2)** (or isoforms/derivatives thereof) site of α-subunit of the $(Na^+ + K^+)$-ATPase (including the α-subunit of one or more isoforms of $(Na^+ + K^+)$-ATPase), comprising:

Please delete paragraph [0037] and replace it with the following paragraph:

[0037] The Jianye-2 peptide (comprising or consisting of sequence RSATEEEPPNDD **(SEQ ID NO: 1)**) as disclosed herein is a particularly preferred peptide. Isoforms (e.g. differing in sequence by 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids, preferably 1, 2, 3, 4, 5, 6, 7 or 8 amino acid differences, more preferably 1, 2, 3, or 4 amino acid differences) of the Jianye-2 peptide also are preferred and those amino acid differences may reflect differences among species.

Please delete paragraph [0038] and replace it with the following paragraph:

[0038] The KX-1 peptide (comprising or consisting of sequence DVEDSYGQQWTYEQR **(SEQ ID NO: 2)**) as disclosed herein is a further particularly preferred peptide. Isoforms (e.g. differing in sequence by 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids, preferably 1, 2, 3, 4, 5, 6, 7 or 8 amino acid differences, more preferably 1, 2, 3, or 4 amino acid differences) of the KX-1 peptide also are preferred and those amino acid differences may reflect differences among species.

Please delete paragraph [0086] and replace it with the following paragraph:

[0086] FIG. 9 is a graph showing the effect of immunization with KX-1 on the rat cardiac heart failure function. The peptide DVEDSYGQQWTYEQR **(SEQ ID NO: 2)** was injected into the animal as a vaccine to reduce the rate of progression of heart failure in the heart failure rat model. TiterMax Gold was used as an adjuvant throughout the experiment. The results show that endogenous KX-1 antibody generation significantly delayed the rate of the progression of heart failure in heart failure rats (red circles). In contrast, cardiac function was significantly depressed in the control heart failure rat without immunization with KX-1 antigen (blue circles).

Please delete paragraph [0087] and replace it with the following paragraph:

[0087] Antibody (Jianye-2 antibody), which recognizes the RSATEEEPPNDD **(SEQ ID NO: 1)** peptide (H1-H2 domain) of the α -subunit of the $(Na^+ + K^+)$-ATPase, and KX-1 antibody which recognizes the DVEDSYGQQWTYEQR **(SEQ ID NO: 2)** peptide (H7-H8 domain) of the α-subunit of the $(Na^+ + K^+)$-ATPase, have been found to increase the contractility of ventricular myocytes which is important in the treatment of muscle contractile disorders.

Please delete paragraph [0089] and replace it with the following paragraph:

[0089] In accordance with the invention, it is preferred that the antibodies specifically bind to peptides having an amino acid sequence RSATEEEPPNDD (SEQ ID NO: 1) (the antibody is referred to herein as the "Jianye-2" antibody), and DVEDSYGQQWTYEQR (SEQ ID NO: 2) (the antibody referred to herein as the "KX-1" antibody), mutants or derivatives thereof. These peptides can be conjugated into polypeptides either directly or through a linker. However, the invention is not limited to these sequences but applies to any sequence in which antibodies can bind resulting in cardiac positive inotropy. The Jianye-2 and KX-1 antibodies are described in detail in the Examples which follow.

Please delete paragraph [0093] and replace it with the following paragraph:

[0093] In another preferred embodiment, the invention provides for pharmaceutical compositions comprising peptides which are administered to patients resulting in the generation of antibodies which recognize such peptides resulting in the in vivo generation of inotropic antibodies. Particularly preferred peptides include, but are not limited to peptides with amino acid sequence RSATEEEPPNDD **(SEQ ID NO: 1)** and/or DVEDSYGQQWTYEQR **(SEQ ID NO: 2)**, mutants and variants thereof.

Please delete paragraph [0097] and replace it with the following paragraph:

[0097] The present invention provides humanized antibody molecules specific for peptides having an amino acid sequence RSATEEEPPNDD **(SEQ ID NO: 1)**, DVEDSYGQQWTYEQR **(SEQ ID NO: 2)** or derivatives thereof. However, the invention is not limited to these sequences but applies to any sequence in which antibodies can bind resulting in cardiac positive inotropy. In accordance with the present invention, the humanized antibodies comprised antigen specific

regions in which at least parts of the CDRs of the heavy and/or light chain variable regions of a human antibody (the receptor antibody) have been substituted by analogous parts of CDRs of a murine monoclonal antibody and the humanized antibody can specifically bind to the same antigen as, for example, the Jianye-2 antibody. In a preferred embodiment of the subject invention, the CDR regions of the humanized Jianye-2 is derived from rabbits as described in the examples which follow. Some of the humanized antibodies described herein contain some alterations of the acceptor antibody, i.e., human, heavy and/or light chain variable domain framework regions that are necessary for retaining binding specificity of the donor monoclonal antibody. In other words, the framework region of some embodiments the humanized antibodies described herein does not necessarily consist of the precise amino acid sequence of the framework region of a natural occurring human antibody variable region, but contains various substitutions that improve the binding properties of a humanized antibody region that is specific for the same target as the Jianye-2 or KX-1 antibodies. A minimal number of substitutions are made to the framework region in order to avoid large-scale introductions of non-human framework residues and to ensure minimal immunogenicity of the humanized antibody in humans. The donor monoclonal antibodies of the present invention Jianye-2 or KX-1 antibodies, which are specific for the rat α-subunit of $(Na^+ + K^+)$-ATPase i.e., RSATEEEPPNDD **(SEQ ID NO: 1)** and DVEDSYGQQWTYEQR **(SEQ ID NO: 2)** peptides respectively.

Please delete paragraph [0142] and replace it with the following paragraph:

[0142] The RSATEEEPPNDD **(SEQ ID NO: 1)** and DVEDSYGQQWTYEQR **(SEQ ID NO: 2)** peptides were synthesized according to the protein sequence reported (Schneider, J. W., Mercer, R. W., Caplan, M., Emanuel, J. R., Sweadner, K. J., Benz, E. J., Levenson, R. (1985) Proc. Natl. Acad. Sci. U.S.A. 82, 6357-6361; Xie, Z., Li, H., Liu, G., Wang, Y., Askari, A., Mercer, R. W. (1994) Cloning of the dog Na/K-ATPase alpha 1 subunit. The Na Pump. (Bamberg, S., and Schoner, W., Eds), pp. 49-52, Springer-Verlag, New York, N.Y.; Shull, M.

M., Lingrel, J. B. (1987) Proc. Natl. Acad. Sci. U.S.A. 84, 4039-4043). The polyclonal Jianye antibody was generated in New Zealand White rabbits using KLH as a peptide carrier (Genemed). The immunoglobulins (IgG) were purified through an affinity column directed against the same synthetic peptide of the $(Na^+ + K^+)$-ATPase. Purified antibodies recognize both denatured (by Western blots) and native $(Na^+ + K^+)$-ATPase (by immunocytostaining). Synthetic peptides were also utilized as the specific peptide blockers for the antibodies.

Please delete paragraph [0158] and replace it with the following paragraph:

[0158] Jianye-2 antibody, which specifically recognizes the RSATEEEPPNDD **(SEQ ID NO: 1)** peptide of the α-subunit of the $(Na^+ + K^+)$-ATPase, has been found to increase the contractility of isolated rat ventricular myocytes. FIG. 1 shows the results obtained with immunofluorescent staining of Jianye-2 antibody in rat cardiac myocytes and African green monkey CV-1 cells. Confocal image of rat cardiac myocytes in the presence of Jianye-2, shown in FIG. 1A or with both Jianye-2 antibody and peptide blocker (FIG. 1B). FIG. 1C shows the immunofluorescent stainings of Jianye-2 antibody in a group of CV-1 cells at a magnification of 400 X FIG. 1D shows the CV-1 cell image at 3000 X Jianye-2 antibody staining in the presence of either 1 mM ouabain (FIG. 1E) or strophanthidin (FIG. 1F). The results reveal that ouabain and strophanthidin compete with the Jianye-2 antibody binding site indicating that Jianye-2 antibody specifically binds to the $(Na^+ + K^+)$-ATPase on the extracellular surface of the cell membrane. FIG. 2 shows results of the time courses of rat heart cell contraction with or without Jianye-2 antibody. Time runs from left to right. Column A, shows the baselines of rat heart cell contraction. Columns B, C, D show the results obtained 10, 20, 30 min after administration of either buffer (upper panel) or Jianye-2 antibody (lower panel, 85 nM). Enzyme activity was monitored in cell homogenates under the same experimental condition. The results show that Jianye-2 antibody enhanced rat heart cell contraction without inhibiting $(Na^+ + K^+)$-ATPase activity. FIG. 3 shows that Jianye-2 antibody markedly increased intracellular Ca.sup.2+ contraction and demonstrates that

intracellular Ca^2 + concentration is involved in the mechanisms of Jianye-2 antibody enhanced heart cell contraction. The data represent a mean of 12 independent experiments. FIG. 4 shows the dose-dependent contractile response of Jianye-2 antibody in rat ventricular myocytes. The half maximal contractile response (EC50) is 35 nM. The data represent a mean of four independent experiments.

Please delete paragraph [0160] and replace it with the following paragraph:

[0160] Antibody (KX-1), which recognizes DVEDSYGQQWTYEQR **(SEQ ID NO: 2)** peptide of α-subunit of the $(Na^+ + K^+)$-ATPase, has been found to increase the contractility of isolated rat heart cells. Vaccination of its specific peptide-antigen in heart diseased animal model significantly decreased the progression of heart failure. This KX-1 antibody, its peptide vaccine, and monoclonal and humanized antibodies are useful for treatment of heart failure and other contractile disorders. FIG. 7 shows that the KX-1 antibody enhanced the velocity of shortening of rat ventricular myocyte and increased the force of contraction of the heart cells. The results indicate that the KX-1 antibody is an inotropic agent.

Please delete paragraph [0161] and replace it with the following paragraph:

[0161] FIG. 8 represents the changes of intracellular calcium transient following the binding of KX-1 to the $(Na^+ + K^+)$-ATPase and indicates that KX-1 induced heart cell contraction is dependent on intracellular Ca^2+ increase. FIG. 9 reveals that the DVEDSYGQQWTYEQR **(SEQ ID NO: 2)** peptide can be utilized as a vaccine to generation of endogenous KX-1 antibody in heart failure rats and the results show that endogenous KX-1 antibody delayed the rate of progression of heart failure in live heart failure rat animal models. In contrast, cardiac function was significantly depressed in the control heart failure rat without immunization with KX-1 antigen.